Remarks/Arguments

The claims have not been amended in the present action. A revised sequence listing that contains only SEQ ID Nos. 1 -3 is submitted with this response. Claims 4 – 8, 10 – 11, 13 – 15 and 36 – 38 remain pending. Reconsideration and withdrawal of the objection and rejections are respectfully requested in light of the amendment to the specification and the following remarks.

A new sequence listing has been submitted to address the Examiner's objection to the specification

The following objection has been rendered moot by amendment:

The Examiner maintained the objection to the specification amendment filed on 11/21/05 that introduced SEQ ID Nos: 4 and 5 into the specification under 35 U.S.C. 132(a). A revised sequence listing that contains only SEQ ID Nos. 1 -3 is submitted with this response. SEQ ID Nos. 4 -5 have been removed from the sequence listing. The paper copy of the sequence listing in this amendment is identical to the ASCII text copy of the sequence listing also filed with this amendment. The content of the present sequence listing does not contain new matter. Incorporation of the sequence listing into the specification is respectfully requested.

Claims 4 – 8, and 36 - 37 are not obvious

The Examiner asserts that claims 4 – 8 and 36 - 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curran et al. (US Patent 6,323,177;"Curran") in view of Keshvara et al (J.Biol. Chem. 276:16008 – 16014, 2001; cited as reference AG2 in the IDS filed on 3/25/02; "Keshvara"), Niethammer et al. (Neuron 28:697 – 711, 2000; cited as reference AM1 in the IDS filed on 3/25/02; "Niethammer"), Carr et al. (Analytical Biochem. 239: 180 – 192, 1996; "Carr") and GenBank Accession Numbers 1771281 and 3288851. The Examiner asserts Curran teaches *in vitro* phosphorylation of Dab1 on serine residues, but acknowledges that Curran does not teach that Dab1 is phosphorylated in a biological sample, e.g., brain and blood. The Examiner asserts Niethammer and Keshvara show various methods for analysis of a phosphoprotein. Niethammer teaches a method for determining the sites of phosphorylation of the Cdk5 substrate polypeptide

NUDEL. Keshvara teaches a method of identifying sites of tyrosine phosphorylation of Dab1 by Src. Carr teaches a method for detecting and sequencing phosphopeptides from an enzymatic digest of a phosphoprotein by mass spectrometry. GenBank Accession Numbers 1771281 and 3288851 disclose the amino acid sequences of murine and human Dab1, respectively. Given the prior art, the Examiner asserts it would have been obvious to one of skill in the art to combine the teaching of Curran, Niethammer, Keshvara and GenBank Accession Numbers 1771281 and 3288851 to immunoprecipitate Dab1 from mouse brain extract with and without catalytically active Cdk5 and analyze its electrophoretic mobility and to determine whether or not serine at position 260, 400, 481, 491, and 515 are phosphorylated by mutating Dab1 serines at such positions to alanine, individually and combinatorially, and **determining the serine(s) that are phosphorylated by Cdk5 in** accordance with the methodology of Niethammer and Keshvara. Alternatively, it would have been obvious to combine Curran, Keshvara and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to **determine its potential sites of phosphorylation** according to the method of Carr. By doing this, one would have practiced the active method steps as recited in the claims. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates serines of Dab1, the sites of Cdk5 phosphorylation of Dab1 can be identified, and may have "significant relevance" to screen for agonists and antogonists because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. According to the Examiner, one would have had a reasonable expectation of success for mutating Dab1 serines at positions 260, 400, 481, 491 and 515 to alanine, individually and combinatorially, and **determining the serine(s) that are phosphorylated by Cdk5** using the methodology of Niethammer and Keshvara because of the results of Curran, Niethammer, Keshvara and GenBank Accession Nos. 1771281 and 3288851. Alternatively, the Examiner asserts that one of ordinary skill in the art would have had a reasonable expectation at the time of the invention to combine the teaching of Curran, Keshvara and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to **determine its potential site(s) of phosphorylation** according to the method of Carr.

Applicants respectfully disagree. The present invention is based on the discovery that Dab1 is selectively phosphorylated by Cdk5 on serines 491 and 515. This discovery is important and non-obvious in that it provides a method for detecting Cdk5 activity in a biological sample which is different from a method for determining which sites in Dab1 are phosphorylated by Cdk5. Before the present invention, a substrate that is selectively phosphorylated by Cdk5 had not been identified. Detection of Cdk5 activity was difficult before the present invention because Cdk5 has to associate with its regulatory subunit, p35, to be activated. Therefore Cdk5 activity cannot simply be determined by measuring the amount of Cdk5 protein present. The discovery that Dab1 is selectively phosphorylated in a biological sample on a serine within a preferred candidate sequence by Cdk5 is the basis for the present invention and is not rendered obvious by the prior art.

As discussed in the previous response to the Office Action dated January 25, 2008, Niethammer suggests serines 491 and 515 as potential sites for cdk (not just Cdk5) activity. None of the prior art references, alone or combined, teach or suggest that specific serines within Dab1 would be a selective target for Cdk5 activity. Until Applicants showed in the present invention that Dab1 is an *in vivo* target of Cdk5, one could not have known or predicted that certain sites in Dab1 would be phosphorylated only by Cdk5 and provide a method for detecting Cdk5 activity. For the reasons set forth above and those more fully outlined on pages 8 – 10 of the previous response to the Office Action dated January 25, 2008, reconsideration and withdrawal of this rejection are respectfully requested.

Claims 10 – 11, 13 – 15 and 38 are not obvious

The Examiner rejected claims 10-11, 13-15 and 38 under 35 U.S.C. 103(a) as being unpatentable over Curran in view of Keshvara, Niethammer, Carr and GenBank Accession Numbers 1771281 and 3288841 as applied to claims 4 – 8 and 36 - 37 above and further in view of Howell et al.(Genes Develop. 13:633 – 648, 1999; cited as reference AY1 in the IDS filed on 3/25/02; "Howell") , Fu et al. (Nature Neurosci. 4:374-381; "Fu"), Michalewski et al. (Analytical Biochem. 276: 254 – 257, 1999; "Michalewski"), and Zhen et al. (J. Neurosci. 21:9160 – 9167, 2001: "Zhen"). These claims limit the claimed methods to detection of Dab1 phosphorylation using an antibody

that binds to Dab1 only when it is phosphorylated on serine or to an antibody generated against SEQ ID NO:3.

Applicants' arguments above show that it was not obvious that Cdk5 serine kinase activity could be determined by determining whether the carboxy terminal domain of Dab1 was phosphorylated on a serine within a candidate sequence. Nothing in the prior art suggests that the serines within a candidate sequence of Dab1, serines 491 and 515, are only phosphorylated by Cdk5. For the reasons stated above, there is nothing in the prior art references of Curran, Keshvara, Niethammer, Carr and the recited GenBank Accession Numbers to suggest the inventions in claims 4-8 and 36-37. Thus combining Howell, Fu, Michalewski and Zhen with Curran, Keshvara, Niethammer, Carr and the recited GenBank numbers does not render the antibodies of claims 10 - 11, 13 -15 and 38 obvious.

Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 10 - 11, 13 - 15 and 38 under U.S.C. 103(a).

Conclusion

It is believed that the objection to the specification and rejections of Claims 4-8, 10-11, 13-15 and 36-38 have been overcome. Reconsideration and withdrawal of the remaining objection and rejections and allowance of all claims are respectfully requested.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 501968.

Respectfully submitted,

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